



## COLON SPECIFIC DRUG DELIVERY SYSTEMS: A REVIEW ON PHARMACEUTICAL APPROACHES WITH CURRENT TRENDS

Cherukuri Sowmya\*, Chappidi Suryaprakash Reddy, Neelaboina Vishnu priya, Reddipalli Sandhya, Komaragiri Keerthi

Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research, Anantapur, Andhra Pradesh, India

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\*E-mail: drsowmyariper@gmail.com

### ABSTRACT

In recent years colon specific drug delivery has gained importance not just for the delivery of drugs for the treatment of local diseases associated with the colon but also as potential site for the systemic delivery of drugs like therapeutic proteins and peptides. This article reviews a detailed study about diseases of colon, diagnosis of diseases of colon, limitations and challenges, applications, anatomy of colon, factors affecting colon and different approaches of colon which include some current new approaches such as Pulsinicap system, Port system, Probiotic approach, Chronotropic system, Colal-pred system, Multiparticulate system, Enterion capsule technology and some past studies of colon drug delivery and also a study on evaluation for site specific drug delivery to colon.

**Key words:** Colon specific drug delivery, Pulsinicap system, Probiotic approach, Enterion capsule technology, Colal-pred system, Past studies.

### INTRODUCTION

At present, various routes of administration have been explored for the effective delivery of drug to the colon. Incorporating an existing medicine into a new drug delivery system can significantly improve its performance in terms of efficacy, safety, and patient compliance. The need for delivering drugs to patients efficiently and with fewer side effects, there is need of development of new drug delivery systems. The oral route is considered to be the most convenient for the administration of drugs to patients. The oral route is considered to be the most convenient for the effective delivery of the drug to colon. On oral administration of conventional dosage forms drug normally dissolves in the gastro-intestinal fluids and is absorbed from these regions of the gastro-intestinal fluids, which depends upon the physicochemical properties of the drug. It has a serious drawback in conditions where localized delivery of the drug in the colon is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT. Dosage forms that deliver drugs in the colon rather than upper GIT has no advantages. Oral delivery of drugs in the colon is valuable in the treatment of diseases of colon (colon cancer, ulcerative colitis, and inflammatory bowel disease) achieving high local concentration minimizing side effects.

Over the past two decades the major challenge for scientist is to target the drugs specifically to the colonic region of GIT. Previously colon was considered as an innocuous organ solely responsible for absorption of water, electrolytes and temporary storage of stools, but now it is accepted as important site for drug delivery. Targeted delivery ensures the direct treatment at the disease site, lower dosing, and minimizing side effects.

Targeting of the drug to the colon is also useful when a delay in drug absorption is desired from a therapeutic point of view, such as treatment of disease that have peak symptoms early in the morning like nocturnal asthma, angina or arthritis. By definition, an oral colonic delivery system should retard drug release in the stomach, small intestine but allow complete release in the colon. The fact that a system will be exposed to diverse range of gastro intestinal conditions on passage

through the gut makes colonic delivery via the oral mouth a challenging position. Targeted drug delivery to the colon therefore ensures direct treatment at the disease site, lower dosing, and fewer systematic side effects. The inability of the GIT enzyme to digest certain plant polysaccharides is taken advantage in developing a colon specific drug delivery system.

Drug targeting into the colon is highly desirable for local treatment of a variety of bowel disease such as ulcerative colitis, crohn's disease, amoebiasis, colonic cancer, local treatment of colonic pathologies, systemic delivery of proteins & peptide drugs.<sup>1,19</sup>

### COLON DISEASES

**Ulcerative colitis:** Ulcerative colitis is a form of inflammatory bowel disease (IBD). It causes swelling, ulcerating loss of function of large intestine. Patients with ulcerative colitis have a significant risk of developing colon cancer. This risk becomes greater every year.

**Crohn's disease:** Crohn's disease is an incurable chronic disease of the intestinal tract, and its sister disorder, Ulcerative colitis are collectively known as Inflammatory bowel disease. Crohn's disease can affect any part of intestinal tract from mouth to the anus. In mild form, crohn's disease cause small scarred shallow craters like areas (erosions) called aphthous ulcers in the inner surface of the bowel. In more serious cases, deeper & larger ulcers can develop, causing scaring and stiffness & possibly narrowing of bowel, sometimes leading to obstruction. Deep ulcers can penetrate holes in the bowel wall leading to infection in the abdominal cavity and in adjacent organs.

**Amoebiasis:** An infection or disease caused by amoebas, especially of the species *Entamoeba histolytica* characterized by dysentery. Amoebiasis most commonly occur in between young to middle aged persons.

**Diverticulosis:** Small weak areas in the colon's muscular wall allow the colon's lining to protrude through, forming tiny pouches called diverticuli. Diverticuli usually cause no problems, but can bleed or become inflamed.

**Diverticulitis:** When diverticuli become inflamed or infected diverticulitis results. Abdominal pain and constipation are common symptoms.

**Colon bleeding (haemorrhage):** Multiple potential colon problems can cause bleeding. Rapid bleeding is visible in the stool, but very slow bleeding might not be.

**Inflammatory bowel disease:** A name for either crohn's disease or ulcerative colitis. Both conditions can cause colon inflammation (colitis).

**Ulcerative colitis:** An inflammatory condition that usually affects the colon and rectum. Like crohn's disease, bloody diarrhoea is common symptom of ulcerative colitis.

**Diarrhoea:** Stools that are frequent, loose or watery are commonly called diarrhoea. Most diarrhoea is due to self-limited, mild infections of the colon or small intestine.

**Salmonellosis:** The bacteria salmonella can contaminate food and infect the intestine. Salmonella causes diarrhoea and stomach cramps, which usually resolve without treatment.

**Shigellosis:** The bacteria shigella can contaminate food and invade the colon. Symptoms include fever, stomach cramps and diarrhoea, which may be bloody.

**Traveler's diarrhoea:** Many different bacteria commonly contaminate water or food in developing countries. Loose stools, sometimes with nausea and fever, are symptoms.

**Colon polyps:** Polyps are small growths. Some of these develop into cancer, but it takes a long time. Removing them can prevent many colon cancers.

**Colon cancer:** Cancer of the colon affects more than 100,000 Americans

#### DIAGNOSIS OF COLON DISEASES

**Colonoscopy:** An endoscope (flexible tube with a camera on its tip) is inserted into the rectum and advanced through the colon. A doctor can examine the entire colon with a colonoscope.

**Virtual colonoscopy:** A test in which an x-ray machine and a computer create images of the inside of the colon. If problems are found, a traditional colonoscopy is usually needed.

**Stool occult blood testing:** A test for blood in the stool. If blood is found in the stool, a colonoscopy may be needed to look for the source.

**Sigmoidoscopy:** an endoscope is inserted into the rectum and advanced through the left side of the colon. Sigmoidoscopy cannot be used to view the middle and right side of the colon.

**Colon biops:** During a colonoscopy, a small piece of colon tissue may be removed for testing. A colon biopsy can help diagnose cancer, infection, or inflammation.<sup>2,3,34</sup>

#### LIMITATIONS AND CHALLENGES IN COLON TARGETED DRUG DELIVERY

- ❖ One challenge in the development of colon specific drug delivery systems is to establish an appropriate dissolution testing method to evaluate the designed system *in vitro*.
- ❖ As a site for drug delivery, the colon offers a near neutral pH, reduced digestive enzymatic activity, a long transit time and increased responsiveness to absorption enhancers; the targeting of drugs to the colon is very complicated. As the colon is situated in the distal part of the Alimentary canal, the colon is particularly difficult to access. In addition to that, the wide range of pH values and different enzymes present throughout the GI tract, through which the dosage form has to travel before reaching the target site, which complicate the reliability and delivery efficiency.

- ❖ The drug to be in solution form before it arrives in the colon for the successful delivery through the site or alternatively, it should dissolve in the luminal fluids of the colon, but this can be a limiting factor for poorly soluble drugs as the fluid content in the colon is much lower and it is more viscous than in the upper part of the GI tract.
- ❖ While designing a drug delivery system, the stability of the drug is also a concern, because it may bind non specific way to dietary residues, intestinal secretions, mucus or faecal matter.
- ❖ Lower surface area and relative tightness of the tight junctions in the colon can also restrict drug transport across the mucosa and into the systemic circulation.<sup>4,38</sup>

#### ANATOMY AND PHYSIOLOGY OF COLON

GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocaecal junction to the anus is divided into three main parts –colon, rectum and the anal canal. In anatomy of digestive system colon primary purpose is to extract water from faeces. In mammals, it consists of the ascending colon on the right side, the transverse colon, the descending colon on the left side, the sigmoid colon, and the rectum. Entire colon is about 5 feet long and 2.5 inches in diameter. It has a moist interior lining that protects nerves located in the colon wall. These nerves send and receive messages to the brain about the colon contents. The brain then directs the appropriate colonic action. Fluids and dietary fibre help to maintain colon health. Colon has a long transit time, near neutral pH, reduced digestive activity and an increased responsiveness to absorption enhancers. The absorbing surface area of the colon is 0.25 m<sup>2</sup>. The usual colonic transit time varies from 20-30 hr. Bacteria live and grows along the colon lining. Using the fluids and foods you intake, bacteria actually manufacture the nutrients that sustain their environment and their food supply. The major function in the colon is the creation of suitable environment for the growth of colonic microorganisms, storage reservoir of faecal contents, expulsion of contents of the colon at an appropriate time and absorption of potassium and water from the lumen.<sup>5</sup>(Fig: 1)

#### COLONIC MICROFLORA:

The sluggish movement of material through the colon allows a large microbial population to succeed there. Over 400 species of bacteria found, for the most part anaerobes and a small number of fungi. The bacterial count (colony for, Peptostreptococcus, Ruminococcus, and Propionibacterium and clostridium unit/mL, CFU/mL) is 10<sup>11</sup>-10<sup>12</sup> CFU/mL in colon. Most of them are anaerobes E.g. Bacteroides, Bifidobacterium, Eubacterium, Peptococcus and other facultative anaerobes e.g. E.coli. Among all of them 20-30 % are Bacteroides.<sup>6,13</sup>

#### ADVANTAGES OF CDDS OVER CONVENTIONAL DRUG DELIVERY:

- Ulcerative colitis and cirrhosis disease are currently treated with glucocorticoids, and other anti-inflammatory agents.
- Utilization of drug is more.
- Side effects can be reduced.
- Lesser amount of dose is required comparatively.<sup>1,19</sup>

#### POLYMERS USED IN COLON TARGETING

Polymers contain a large no of structural units joined by same type of linkage, form into a chain like structure. These are used now-a-days in formulating various pharmaceutical products. Naturally found polymers, which includes gummy

exudates, proteins, enzymes, muscle fibre, polysaccharides. In olden days natural polymers are widely used in pharmacy, but a variety of synthetic polymers are used now-a-days for pharmaceutical and cosmetic development. Using these polymers many therapeutic systems of body namely controlled drug delivery systems are achieved.

#### Natural polymers

Guar gum, pectin, inulin, locust bean gum, cyclodextrins, dextran, chondroitin sulphate, boswellia gum, amylase, chitosan.

#### Synthetic polymers

Shellac, Ethyl cellulose, cellulose acetate phthalate (cellacefat), hydroxy propyl methyl cellulose, polyvinyl acetate phthalate, Eudragits, Hydroxy propyl methyl cellulose acetate succinate (HPMCAS),<sup>8,9,10,13</sup>

### FACTORS AFFECTING COLONIC DRUG DELIVERY

There are many factors that influence the drug delivery to colon.

#### 1. Transit through GI tract

Drug delivery systems enter into stomach and small intestine via mouth and then reach colon. The nature and pH of gastric secretion and gastric mucus influence the drug release and absorption. To reach the colon in an intact form, the drug delivery system should bypass the barriers in the stomach and small intestine. GI transit varies from 1-3 hours depending upon fasting or non fasting condition. In general, small intestinal transit is not influenced by the physical state, size of the dosage form and presence of food in the stomach. The mean transit time required for the dosage form to reach the ileocaecal junction is 3-4 hours and the time period is inconsistent. During the transit time period the dosage form is exposed to enzymes (such as esterase, amylase, lipase, protease, nuclease, glycosidase and disaccharidases etc.) present in the small intestine. The bioavailability of drugs can be highly influenced by colonic transit time. Compared with the other regions of GI tract, movement of material through the colon is slow and influenced by no of factors such as diet, dietary fibre content, mobility, stress, disease condition and drugs. The colonic transit time of a capsule in an adult is 20-35 hours. Release and absorption of drug from dosage form are governed by improved residence time with longer transit time and contact of dosage form with microflora in colon.

#### 2. Gastric emptying

After entering the dosage form into stomach, the main concern is how long it remains there before being discharged into the duodenum. Depending on the phase of the stomach at the time of administration emptying generally completes from 5-10 min up to 2 hours. It is preferable for a colonic drug delivery system to reside for a little time in the system because such system releases the drug at a distant locus from the colon.

#### 3. Stomach and intestinal pH

The pH of GI tract must be considered when enteric coatings or bioerodible polymers are used to deliver the drugs to colon because in such systems, GI tract pH gradient is used to trigger drug release. The pH of the GI tract is subjected to both inter and intra subject variation. (Table: 1)

#### 4. Colonic microflora

The human Alimentary canal is highly populated with bacteria and microflora at both ends, i.e. oral cavity and colon/rectum, in between these two very less populated with microorganisms and microorganisms of oral cavity do not normally affect oral drug delivery. The colonic bacteria are predominately anaerobic in nature and secrete enzymes that are capable of metabolizing substrates such as carbohydrates

and proteins that escape the digestion in the upper GI tract [6-8]. Bacterial count in colon is much higher around 10<sup>11</sup>-10<sup>12</sup> CFU/ml with some 400 different species which are fundamentally aerobic, predominant species such as Bacteroides, Bifidobacterium and Eubacterium etc., whose major metabolic process occurring in colon are hydrolysis and reduction. The enzymes present in the colon are:

- **Reducing enzymes**

Nitroreductase, Azoreductase, N-oxide reductase, sulfoxide reductase, Hydrogenase.

- **Hydrolytic enzymes**

Esterases, Amidases, Glycosidases, Glucuronidase, sulfatase etc.

### 5. Gastrointestinal disease state

Intestinal diseases like crohn's disease, Inflammatory Bowel Disease (IBD), constipation, diarrhoea and gastroenteritis affect the drug release and absorption properties of drugs from colon specific drug delivery system.<sup>7,11,13</sup>

### APPLICATIONS OF COLON DRUG DELIVERY SYSTEM

- Targeted drug delivery to the colon ensures direct treatment at the disease site, lower dosing and fewer systemic side effects.
- To prevent asthma, arthritis attacks in the early morning.
- To delay the drug absorption.
- Colon drug delivery system is considered to be beneficial in the treatment of colon diseases.
- Colon is a site where local and systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, for example Ulcerative colitis or crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine.
- Site specific drug delivery would allow oral administration of protein and peptide drugs, colon-specific formulation could also be used to prolong the drug delivery.
- Formulations for colonic delivery are also suitable for delivery of drugs which are polar and susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.
- Other serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively, if drugs were targeted to the colon.<sup>12,13</sup> (Table:2)

### PHARMACEUTICAL APPROACHES TO DELIVER A DRUG TO COLON

#### I. COVALENT LINKAGE OF A DRUG WITH A CARRIER<sup>14,39</sup>

##### Prodrug approach

Formation of a covalent linkage between drug and carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine. Prodrug, which is a pharmacologically inactive derivative of a parent drug molecule, requires spontaneous (or) enzymatic transformation in the biological environment to release the active drug. Site specific drug delivery through site specific prodrug activation may be accomplished by utilization of some specific property at the target site, such as altered or high activity of certain enzymes relative to the non-target tissues for the prodrug-drug conversion.<sup>12, 14</sup>

##### Azo bond conjugates

In this type of conjugation drug is conjugated with an azo bond to the carrier. These azo compounds are extensively

metabolized by the intestinal bacteria, both by intracellular enzymatic component and extracellular reduction. This azo bond is stable in the upper GIT and is cleaved in the colon by the azo-reductases produced by the microflora.

Ex: Sulphasalazine is introduced for the treatment of rheumatoid arthritis and anti-inflammatory disease. Chemically it is salicylazosulphapyridine (SASP), where sulphapyridine is linked to a salicylate radical by an azo bond. When taken orally, only a small proportion of the ingested dose is absorbed from the small intestine and the bulk of the sulphasalazine reaches the colon intact. After reaching the colon there is split at the azo bond by the colonic bacteria with the liberation of sulphapyridine and 5-ASA. Some new approaches for the treatment of IBD have emerged due to the side effects of sulphasalazine. This is done by replacing the carrier molecule with others such as P-aminohippurate (4-amino benzoyl glycine) in ipsalazine, 4-amino benzoyl-  $\beta$ - alanine in balsalazine, p-aminobenzoate in HB-313 or a non-absorbable sulphanilamide ethylene polymer in poly-ASA. The most important prodrug is olsalazine (OSZ) which is a dimer having two molecules of 5-ASA that are linked via an azo bond.<sup>7,15,16,22</sup> (Fig: 2)

#### **Glycoside conjugates**

Steroid glycosides and the unique glycosidase activity of the colonic microflora form the basis of a new colon targeted drug delivery system. Drug glycosides are hydrophilic and thus, poorly absorbed from the small intestine. Once such a glycoside reaches the colon it can be cleaved by bacterial glycosidases, releasing the free drug to be absorbed by colonic mucosa. The major glycosidase enzymes produced by the intestinal microflora are  $\beta$ -D-galactosidase,  $\alpha$ -L-arabinofuranosidase,  $\beta$ -D-xylopyranosidase, and  $\beta$ -D-glucosidase. These glycosidase enzymes are located at the brush border and hence are accessible to substrate easily. Various naturally occurring glycosides, e.g. the sennosides, have been used for laxative action for ages. Friend and Chang prepared dexamethasone-21-  $\beta$ -glucoside and prednisolone-21-  $\beta$ -glucoside for delivery of these steroids to the colon.<sup>17,22</sup>

#### **Glucuronide conjugates**

Glucuronide and sulphate conjugation is the major mechanisms for the inactivation and preparation for clearance of a variety of drugs. Bacteria of the lower GIT however secrete  $\beta$ -glucuronidase and can deglucuronidate a variety of drugs in the intestine.<sup>15,22</sup>

#### **Cyclodextrin conjugates**

Cyclodextrin (CYDs) are cyclic oligosaccharides which consists of 6 to 8 glucose units through  $\alpha$ -1,4 glucosidic bonds and utilized to improve certain properties of drugs such as solubility, stability and bioavailability. These are water soluble cyclic carbohydrate compounds and the interior of these molecules is lipophilic and exterior hydrophilic, and tend to form inclusion complexes with various drug molecules. They are only slightly absorbed in passage through the stomach and small intestine; however they are fermented by colonic microflora into small saccharides and thus absorbed in large intestine. Because of their bioadaptability and multi-functional characteristics, these are capable of alleviating the undesirable properties of drug molecules in various routes of administration through the formation of inclusion complexes. In an oral drug delivery system the hydrophilic and ionisable CyDs can serve as potent drug carriers in the immediate release and delayed release formulations while hydrophobic CyDs can retard the release rate of water soluble drugs.<sup>14, 22, 33</sup>

#### **Dextran conjugates**

Dextran is a complex, branched glucan made of many glucose molecules joined into chains of varying lengths. This is synthesized from sucrose by lactic acid bacteria. The enzyme responsible for the hydrolysis of the linkages is dextranase. Activity of this enzyme is almost absent in the upper GIT, where as high dextranase activity is shown by anaerobic gram negative bacteria, especially the bacteroides, this led to the use of dextran as carriers for drug molecules to the colon. Dextran is a carbohydrate which is used to prepare hydrogel type of biodegradable and biocompatible systems. Enzymatic cleavage has been applied to the colon site specific delivery of drugs by forming ester type macromolecular prodrugs of carboxylic acids containing drugs like naproxen with drugs. Ex. Dextran ester prodrug was prepared and in vitro release of naproxen from prodrug was several folds higher in caecum homogenates of the small intestine of pig. The bioavailability of naproxen after oral administration of a dextran T-70-naproxan ester prodrug in pigs was assessed by Harboe et al. Compared to the administration of a oral solution of an equivalent dose of naproxen the average absorption fraction for the conjugate amounted to 91%.<sup>12</sup>

#### **Amino acid conjugation**

Due to the hydrophilic groups like  $-\text{NH}_2$  and  $-\text{COOH}$ , that is present in proteins and their basic units (amino acids), they reduce the membrane permeability of aminoacids and proteins. By the conjugation of drug molecules to these polar aminoacids various prodrugs have been prepared. The prodrug was absorbed into the systemic circulation from the upper GIT and hence it was proved unsuitable for delivery of drugs to the colon. By increasing the hydrophilicity and chain length of the carrier aminoacid and decreasing the membrane permeability of conjugate. This conjugate showed splendid results with minimal absorption and degradation in the upper GIT and proved suitable for colon targeted delivery.<sup>14</sup>

#### **Polymeric prodrugs**

Use of naturally occurring polysaccharides is attracting a lot of attention for drug targeting the colon since these polymers of monosaccharides are found in abundance, have wide availability, inexpensive and are available in a variety of structures with varied properties. They can be easily modified chemically, biochemically, and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition are biodegradable. These include naturally occurring polysaccharides obtained from plant (guar gum, inulin, pectin), animal (chondroitin sulphate), algal (alginates) or microbial (dextran) origin. The polysaccharides are broken down by colonic microflora to simple saccharides.<sup>22</sup>

## **II. APPROACHES TO DELIVER THE INTACT MOLECULE TO THE COLON**<sup>22, 39</sup>

#### **Coating with polymers**

The intact molecule can be delivered to the colon without absorbing at the upper part of the intestine by coating of the drug molecule with the suitable polymers, which degrade only in the colon.

#### **Coating with pH sensitive polymers**

pH of the human GIT increases progressively from the stomach (pH 1-2 which increases to 4 during digestion), small intestine (pH 6-7) at the site of digestion and it increases to 7-8 in the distal ileum. The coating of pH-sensitive polymers to the tablets, capsules or pellets provide delayed release and protect the active drug from gastric fluid. Use of pH dependent polymers is based on the differences in pH levels. The polymers described as pH dependent in colon

specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. Although a pH dependent polymer can protect a formulation in the stomach, and proximal small intestine, it may start to dissolve in the lower small intestine, and the site-specificity of formulations can be poor. The decline in pH from the end of the small intestine to the colon can result in problems, lengthy lag times at the ileocaecal junction or rapid transit through the ascending colon which can also result in poor site-specificity of enteric-coated single-unit formulations. Commonly used co-polymers of methacrylic acid and methyl methacrylate have been extensively used for colonic drug delivery systems. An important limitation of the pH sensitive coating technique is the uncertainty of the location and environment in which the coating may start to dissolve. It is possible that enteric coating alone may lead to premature drug release in the small intestine due to a variation in GI motility in individual patients and in different disease states. Occasionally, failure of the coating to dissolve may also occur particularly when the pH of the colon and possibly the small intestine drops below normal in patients with ulcerative colitis. These issues have prompted the development of other types of delivery systems.<sup>22, 39</sup> (Table 3)

#### **Coating with biodegradable polymers**

Biodegradable azo polymers with high hydrophilicity exhibit superior degradation properties and are used to coat capsules. The azo polymer systems are not suitable for delivery of peptides, hormones and other drugs with a narrow therapeutic index; however they are suitable for local delivery of drugs to the colon. Most commonly used polymers are methacrylic acid co-polymers commonly known as Eudragit L and Eudragit S. Carboxyl polymer form salts and dissolves at pH 5.5 and disperse in water to form latex and thus avoid the use of organic solvents in the coating processes.<sup>22, 39</sup> The principle of biodegradable polymer is shown in (Fig: 3)

#### **Embedding in matrices**

The drug molecules are embedded in the polymer matrix. Polymers used for this technique should exhibit degradability in the colon for liberation of entrapped drug.

#### **Embedding in pH sensitive matrices**

The drug molecules are embedded in the polymer matrix. Extrusion spherulization technique can be used to prepare uniform-size study pellets for colon targeted drug delivery, when it is not possible to obtain mechanically strong granules by other methods.<sup>22</sup>

#### **Embedding in biodegradable matrices and hydrogels**

Polysaccharides, the polymer of monosaccharides retains their integrity because they are resistant to the digestive action of gastro intestinal enzymes. The matrices of polysaccharides remain intact in the physiological environment of stomach and small intestine but once they reach in colon they are acted upon by the polysaccharides and results in the degradation of matrices. A large number of polysaccharides such as amylose, guar gum, pectin, inulin, chitosan, cyclodextrins, chondroitin sulphate, dextrans and locust bean gum have been investigated for their use in colon targeted drug delivery systems. The most important fact in the development of polysaccharide derivatives for colon targeted drug delivery is the selection of a suitable biodegradable polysaccharide. As these polysaccharides are usually soluble in water, they must be made water insoluble by crosslinking or hydrophobic derivatization. Optimal proportion of the hydrophobic and hydrophilic parts respectively and number of free hydroxyl groups in the polymeric molecule is very important.<sup>22, 33</sup>

#### **Timed release systems**

The basic principle involved in the system is that the release of drug from dosage form should be after a predetermined lag time to deliver the drug at the right site of action at right time and in the right amount. It is also known as pulsatile release, delayed or sigmoidal release system. This approach is based on the principle of delaying the release of the drug until it enters into the colon. The disadvantages of this system are:

1. Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.
2. Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.
3. Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhoea and the ulcerative colitis.

Combination of hydrophilic (HPMC) and hydrophobic polymers has been used as coatings for tablets that release the drug from a core after a lag time.<sup>22, 34</sup> (Fig: 4)

#### **Redox-sensitive polymers**

Analogues to azo bond cleavage by intestinal enzymes, novel polymers that hydrolyzed non enzymatically by enzymatically generated flavins are being developed for colon targeting. It is suggested that both an intracellular enzymatic component and extra cellular reduction exists. Under anaerobic conditions, bacterial azo reduction by enzymatically generated reduced flavins where the initial substrate thought to be involved in cellular electron transport requires the presence of NADPH as its electron source. As NADPH is oxidised the electron mediator (reduced flavins) acts as an electron shuttle from the NADPH dependent flavoprotein to the azo compound. Molecular modelling of low molecular weight azo compounds revealed that reduction of the azo bond to the hydroazo intermediate requires a low electron density within the azo region, and thus substitution of electron withdrawing groups will favour this reaction.<sup>34</sup>

#### **Bio adhesive systems**

Oral administration of some drugs requires high local concentration in the large intestine for optimum therapeutic effects. Bioadhesion is a process by which a dosage form remains in contact with particular organ for an augmented period of time. This longer residence time of drug would have high local concentration or improved absorption characteristics in case of poorly absorbable drugs. This strategy can be applied for the formulation of colonic drug delivery systems. Various polymers including polycarboxylics, polyurethanes and polyethylene oxide, polypropylene oxide copolymers are used as materials for bioadhesive systems. Bio adhesion has been proposed as a means of improving the performance and extending the mean residence time of colonic drug delivery system.<sup>35, 38</sup>

#### **Osmotic controlled drug delivery**

The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4mm in diameter, encapsulated within a hard gelatin capsule. Each push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semi permeable membrane. An orifice is drilled into the semi permeable membrane to the drug layer. The outside surface of the semi permeable membrane is coated with Eudragit S 100 to delay the drug release from the device during its transit through the stomach. Upon arrival on the small intestine the coating dissolves at  $\text{pH} \leq 7$ . As a result water enters the unit causing the osmotic

push compartment to swell forcing the drug out of the orifice into colon.<sup>19,36</sup> (Fig: 5)

### III. CURRENT APPROACHES

#### Pulsinacip system

Single unit formulations are mostly developed in a capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion and the drug is released as a "pulse" from the insoluble capsule body. Such systems comprises of a water insoluble capsule enclosing the drug reservoir. A swellable hydrogel plug was used to seal the drug contents into the capsule body. When this capsule comes in contact with the dissolution fluid, it swells and after a lag time, the plug pushed itself outside the capsule and rapidly releases the drug. Polymers used for the hydrogel plug were different viscosity grades of hydroxyl propyl methyl cellulose, poly vinyl acetate, poly methyl Methacrylate and polyethylene oxide. The length of the plug and its point of insertion into the capsule controlled the lag time.<sup>20,21,27</sup> (Fig: 6, 7)

#### Port system

The port system consists of a capsule coated with a semi permeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation. When this capsule comes in contact with the dissolution fluid, the semi permeable membrane allow the entry of water leading to the pressure development inside the capsule and the insoluble plug expelled after a lag time. The dosage form is designed in such a manner that after ingestion, the first drug release pulse occurs within 1-2 hr, followed by period during which no release occurs. Second dose is released in 3-5 hr of ingestion. This is again followed by a second no release interval. Release of third dose occurs within 7-9 hr of ingestion. This system avoids the second time of dosing.<sup>21</sup> (Fig: 8)

#### Probiotic approach

The probiotic approach is one of the latest approaches for colon targeting. In approach, three components are desirable namely probiotic strain, microbially digestible carrier and triggering temperature. Probiotic strains include inactive microflora like Bifidobacterium and Lactobacillus species. At body temperature, these strains triggered to be active and start digesting the carrier and ultimately release the drug at desired place. This approach gains success in colon drug delivery system because these conditions are only available in colon. Ghosh et al. performed this approach for Diclofenac sodium using guar gum as the carrier in matrix tablets. They gained success as the formulation containing probiotics show better release of drug alone in carrier.<sup>23</sup>

#### Chronotropic system

These systems are based upon a drug reservoir surrounded with a soluble barrier layer that dissolves with time and drug releases at once after this lag time, Chronotropic system consists of a core containing reservoir coated by a hydrophilic polymer outside this layer to overcome intra subject variability in Gastric emptying rate.<sup>24,39</sup> (Fig: 9)

#### COLAL-PRED system

COLAL-PRED is a proprietary gastrointestinal product developed by Alizyme for the treatment of ulcerative colitis (US). It has arisen from combining Alizyme's proprietary colonic drug delivery system, COLAL, with an approved generic steroid (Prednisolone sodium metasulfobenzoate). It is an effective anti inflammatory treatment for UC without the typical side effects of steroids. There are currently no competitor products, either on the market or in development, with the same profile of product. A 'safe steroid' product

with the profile of COLAL-PRED would represent a significant advance in the management of UC. COLAL-PRED has a coating that is broken down only in the colon, by locally occurring bacteria. This leads to topical delivery of prednisolone to the colon without significant systemic exposure so minimizing steroid related side effects.<sup>25</sup>

#### Multiparticulate system

Recently, much emphasis is being laid in the development of multiparticulate dosage forms in comparison to single unit systems because of their potential benefits like increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying. Multiparticulate approaches tried for colonic delivery include the formation of pellets, granules, microparticles and nanoparticles. The use of multiparticulate drug delivery system is preferred to single unit dosage forms as it has been observed that multiparticulate systems enabled the drug to reach the colon quickly and were retained in the ascending colon for a relatively long period of time. These systems are capable of passing through the GIT easily due to their smaller particle size as compared to single unit dosage forms, leading to less inter and intra subject variability. Moreover, mutiparticulate systems tend to be more uniformly dispersed in the GIT that ensures more uniform drug absorption. Most commonly used multiparticulate systems for colon specific drug delivery include pellets, granular matrices, beads, microspheres and nanoparticles.<sup>35</sup> (Fig: 10)

#### Nanoparticulate system

Nanoparticle size colloidal carriers composed of natural or synthetic polymers have also been investigated for colon targeting. Orally administered nanoparticles such as carriers for different types of drugs have been shown to enhance their solubility, permeability and bioavailability. Nanoparticles have also been investigated for the delivery of protein and peptide drugs. The use of nanoparticles for bioadhesion purposes has also been investigated. Nanoparticles have a large specific surface, which is indicative of high interactive potential with biological surfaces. Since the interaction is of nonspecific nature, bioadhesion can be induced by binding nanoparticles with biological surfaces. For covalent attachment, the nanoparticle surface has to show free functional groups, such as carboxylic or amine residues.<sup>27</sup>

#### Enterion capsule technology

The Enterion capsule has recently been developed by Phacton Research, Nottingham, UK, for targeted delivery of a wide range of different drug formulations into any region of the gut. It is a 32-mm long, round-ended capsule and contains a drug reservoir with a volume capacity of approximately 1 ml. The capsule can be loaded with either a liquid formulation (e.g. Solution, suspension) or a particulate formulation (e.g. powder, pellets) through an opening 9 mm in diameter, which is then sealed by inserting a push-on cap fitted with a silicone O-ring. The floor of the drug reservoir in the piston face, which is held back against a compressed spring by a high tensile strength polymer filament. A radioactive marker is placed inside a separate sealed tracer port to allow real time visualization of the capsule location using the imaging technique of  $\gamma$ - Scintigraphy. When the capsule reaches the target location in the gastrointestinal tract, the contents are actively ejected by the external application of an oscillating magnetic field. The frequency of the magnetic fluid is set in the low MHz region, low enough so that there is negligible absorption of the energy by the body tissues but sufficiently high enough to induce unable power in a tuned coil antenna

embedded in the capsule wall. The power induced in the coil by the magnetic field is fed to a tiny heater reservoir located within a separate sealed electronics compartment inside the capsule. Although the power is only a few tenths of a watt, the small size of the heater (less than 1 mm<sup>3</sup>) means that heat build up is extremely rapid. The heater resistor is in direct contact with the restraining filament, causing it to soften and break with the increase in temperature. This in turn, releases the spring and drives the piston. The resulting increase in pressure within the drug reservoir forces the O-ring sealed cap and rapidly ejects the drug or drug formulation into the surrounding GI fluids. The piston motion is stopped near the end of the capsule, which maintains a seal and prevents contact of the internal electronic compartments with the GI fluids. The movement of the piston also operates a switch, which directs some of the electrical energy away from the heater and uses it to transmit a weak radio signal at a precise frequency. Detection of this signal externally confirms that the capsule has opened successfully.<sup>28</sup> (Table: 4)

#### **EVALUATION OF COLON SPECIFIC DRUG DELIVERY SYSTEM:**

The drug release in the colonic region from different colon drug delivery systems is evaluated by different methods of *in vitro* and *in vivo* release studies, which show the success rate of different designs of CDDS. Depending upon the method of preparation different evaluation methods are proposed. A successful colon specific drug delivery system is one of that remains intact in the physiological environment of stomach and small intestine, but releases the drug in the colon.<sup>29, 30, 32, 37</sup>

#### **In vitro dissolution test**

Dissolution testing has been an integral component in pharmaceutical research and development of solid dosage forms. It provides decisive information on formulation selection, the critical processing variables, *in vitro/in vivo* correlation and quality assurance during clinical manufacturing. In order to provide this information, dissolution testing should be conducted in physicochemically and hydrodynamically defined conditions to simulate the environment that the dosage form encounters in the GI tract. Currently, four dissolution apparatus are recommended in the USP to accommodate different actives and dosage forms: basket method, paddle method, Bio-Dis method and flow-through cell method. However certain constraints associated with USP dissolution methods were recognised in the dissolution evaluation of complex controlled release drug delivery systems for oral application, and modification of USP dissolution methods to evaluate such delivery systems was deemed necessary. As described above various mechanisms have been incorporated into colon specific delivery systems. Conventional dissolution testing proposed in USP appears unable to discriminate drug release from systems with different triggering mechanisms. For *in vitro* evaluation of colon specific drug delivery systems, the ideal dissolution testing should closely mimic the *in vivo* conditions with regard to pH, bacteria, and types of enzymes, enzymatic activity, fluid volume and mixing intensity. Apparently such dissolution specifications will be very difficult, if possible at all, to be standardized and validated.

In *in-vitro* studies the ability of the coats/carriers to remain intact in the physiological environment of the stomach and small intestine is assessed by drug release studies in 0.1N HCl for two hours (mean gastric emptying time) and in pH 7.4 phosphate buffer for three hours (mean small intestine transit

time) using USP dissolution apparatus. In case of microflora activated system dosage form, the release rate of drug is tested *in vitro* by incubating in a buffer medium in the presence of either enzymes (e.g., pectinase, dextranase) or rat/guinea, pig/rabbit caecal contents. The amount of drug released at different time intervals during the incubation is estimated to find out the degradation of the carrier under study.<sup>29, 31</sup>

#### **In-vivo Evaluation**

As in other controlled release delivery systems, the successful development of a colon-specific drug delivery system is ultimately determined by its ability to achieve colon-specific drug release and thus exert the intended therapeutic effect. When the system design is conceived and prototype formulation with acceptable *in vitro* characteristics is obtained, *in vivo* studies are usually conducted to evaluate the site specificity of drug release and to obtain relevant pharmacokinetics information of the delivery system. Although animal models have obvious advantages in assessing colon-specific drug delivery systems, human subjects are increasingly utilized for evaluation of this type of delivery systems with visualization techniques such as  $\gamma$ -scintigraphy imaging.

#### **Animal studies**

A number of animals such as dogs, guinea pigs, rats and pigs are used to evaluate the delivery of drug to colon because they resemble the anatomic and physiological conditions as well as the micro flora of human GIT. While choosing a model for testing a CDDS, relative model for the colonic diseases should also be considered. Guinea pigs are commonly used for experimental IBD model. The distribution of azoreductase and glucuronidase activity in the GIT of rat and rabbit is fairly comparable to that in the human. For rapid evaluation of CDDS, a novel model has been proposed. In this model, the human foetal bowel is transplanted into a subcutaneous tunnel on the back of thymic nude mice, which vascularises within four weeks, matures, and becomes capable of developing of mucosal immune system from the host.

#### **$\gamma$ - Scintigraphy**

With growing complexity in the design of novel drug delivery systems (including colon-specific delivery systems) and associated fabrication process, it is critical to understand the *in vivo* performance of those delivery systems and demonstrate that the system functions *in vivo* in accordance with the proposed rationale. In most cases, conventional pharmacokinetic evaluation may not generate sufficient information to elucidate the intended rationale of system design.  $\gamma$ - Scintigraphy is an imaging modality, which enables the *in vivo* performance of drug delivery system to be visualized under normal physiological conditions in a non-invasive manner. Through  $\gamma$ -Scintigraphy imaging, the following information regarding the performance of a colon specific delivery system within human GI tract can be obtained, the location as a function of time, the time and the location of initial and complete system disintegration, the extent of dispersion, the colon arrival time, stomach residence and small intestine transit times. E.g. study of placebo CODES<sup>TM</sup> was conducted in eight male healthy volunteers to ascertain the time and location of tablet disintegration in the GI tract by using the radio labelled resin incorporated in the core tablet.

#### **Drug delivery index (DDI) and clinical evaluation of colon-specific drug delivery systems**

DDI is a calculated pharmacokinetic parameter, following single or multiple dose of oral colonic prodrugs. High drug

DDI value indicates better colon drug delivery. Absorption of drugs from the colon is monitored by colonoscopy and incubation. Currently, gamma scintigraphy and high frequency capsules are the most preferred techniques.<sup>30, 32</sup>

$$DDI = \frac{\text{Relative colonic tissue exposure to the drug (RCE)}}{\text{Relative system exposure to the drug (RSC)}}$$

## CONCLUSION

The most critical challenge in oral colon specific drug delivery approach is to preserve the formulation during its passage through the stomach and about 6 m of small intestine. Successful colonic delivery could be achieved by protecting the drug from absorption (or) the environment of the upper GIT and then be abruptly released into the proximal colon, which is considered the optimum site for colon targeted delivery of drugs. There is a constant need for new drug delivery systems that can provide increased therapeutic benefits to the patients. Colon targeted drug delivery systems are one such systems that, by delivering drug at the right time, right place and in right amount holds good promises of benefits to the patients suffering from chronic problems.

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**Table:1-Stomach and Intestinal pH**

Region	pH
Stomach(before meal)	1-2
Stomach (during digestion) <sup>4</sup>	4
Small intestine	6-7
Duodenum	6.6+0.5
Ileum	7.5+0.4
Caecum	6.4+0.4
Colon	5.5-7
Rectum	7

**Table: 2 Criteria for selection of CDDS**

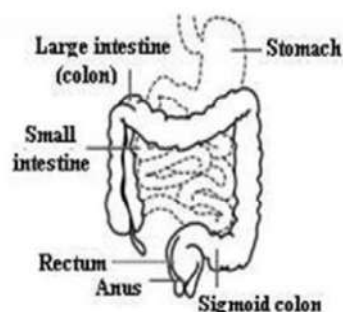
Criteria	Pharmacological class	Drug candidate	
		Peptide drugs	Non-peptide drugs
1.Drugsfor colon cancer	Antineoplastic drugs	Glucagon, Epoetin	Pseudoephedrine
2.Drugs poorly absorbed from upper GI tract	Antianginal and Antihypertensive drugs	Cyclosporin, Desmopressin	Isosorbides, Ibuprofen, Theophylline.
3.Drugs used for local effects in colon against GI tract diseases.	Anti-inflammatory drugs	Calcitonin, Amylin, Antisense oligonucleotide.	Sulfasalazine, Olsalazine, Oxyprenolol, Metaprolol, Diclofenac sodium, Nifedipine, Mesalazine.
4.Drugs that degrade in stomach and small intestine.	Protein and peptide drugs	Insulin, Interferons	5-Fluorouracil, Doxorubicin, Bromophenaramine.
5.Drugs that undergo extensive first pass metabolism	Corticosteroids and Nitroglycerine	Protirelin, Sermorelin, Molgramoatim, Soloatonin.	Bleomycin, nicotine, Dexamethasone.
6.Drugs for targeting	Antiasthmatic and Antiarthrositic drugs	Somatropin, Vasopressin	Hydrocortine, 5-Amino salicylic acid, Prednisolone.

**Table:3- Threshold pH of commonly used polymers**

Enteric polymer	Threshold pH
Eudragit L 100	6.0
Eudragit S100	7.0
Eudragit L 30D	5.6
Eudragit FS 30D	6.8
Shellac	7.0
Poly vinyl acetate phthalate	5.0
Cellulose acetate phthalate	5.5
Hydroxy propyl methyl cellulose phthalate(HPMCP)	5.5
Hydroxy propyl methyl cellulose acetate succinate(HPMCAS)	6.0
Methacrylic acid copolymer(Type A)	6.0
Methacrylic acid copolymer(Type C)	6.0
Methacrylic acid copolymer dispersion	5.5

**Table:4- List of few studies using different technologies**

Carrier used	Technology	Reference
L-Histidine	Mutual azo prodrug of 5-ASA	Deepika Nagpal et al(2006) <sup>40</sup>
Carboxymethyl high amylose starch:chitosan	Probiotic approach	Carmen calinescu et al(2008) <sup>41</sup>
Novel polymeric film coating	Coated pellets	Christel Neut et al(2009) <sup>42</sup>
Poly(lactic co-glycolic) acid(PLGA) and a pH sensitive Methacrylate polymer	pH sensitive nanospheres	Abdulla Makhlof et al(2009) <sup>43</sup>
Ligand appended polysaccharide	Nanoparticles	Anekant Jain et al(2010) <sup>44</sup>
Pectin:HPMC mixture	Microsponges compressed to tablet	Vikas Jain et al (2011) <sup>45</sup>
Konjac-glucomannan	Pulsatile delivery	Jing Liu et al(2012) <sup>46</sup>

**Fig: 1-Anatomy of Human intestine**

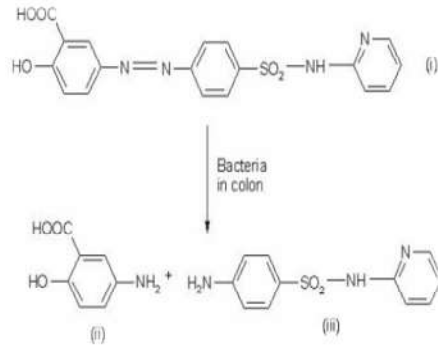


Fig:2- Hydrolysis of sulfasalazine (i) into 5-amino salicylic acid (ii) and sulfapyridine (iii)

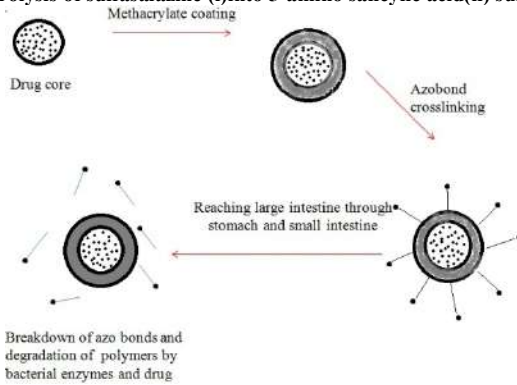


Fig:3- Working principle of biodegradable azo polymer systems

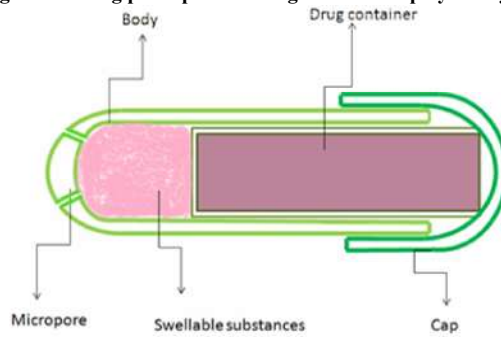


Fig:4-Time controlled (or) Time dependent system

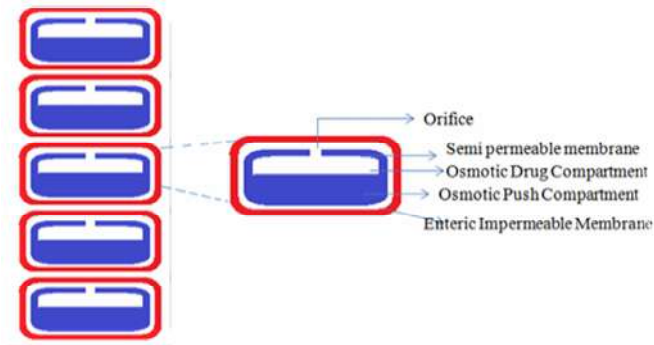


Fig:5-Cross-section of the OROS-CT colon targeted drug delivery system

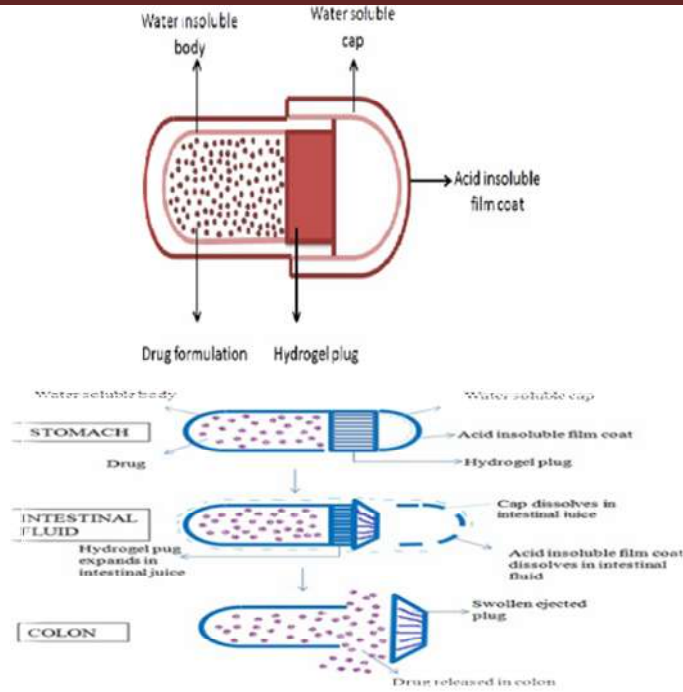


Fig:6,7- Design of Pulsinicap system  
Drug release mechanism from PORT system

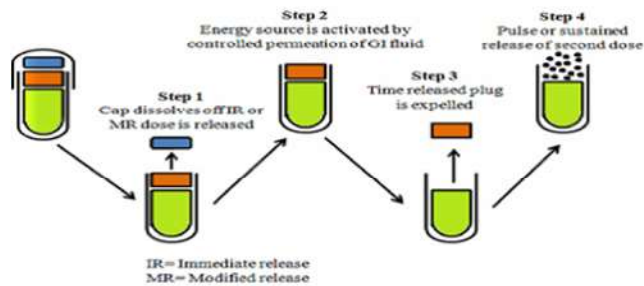


Fig: 8- Design of Port system

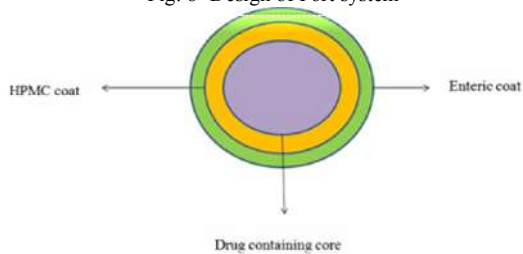


Fig: 8- Design of Chronotropic system

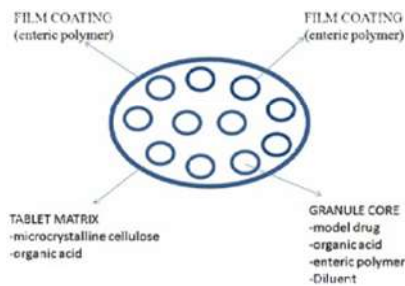


Fig: 8- Design of Multiparticulate system